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STUDY ON THE NEURONAL CIRCUITS IMPLICATED IN POSTURAL TREMOR AND HYPOKINESIA[1]

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Introduction

In monkeys, parkinsonian type tremor caused by pontomesencephalic /15* ventromedian tegmentary lesions (Ward, McCullogh and Magoun, 1948; Poirier, 1960) corresponds closely to that reported in man following pathological processes involving the same region (Kremer, Russel and Smith, 1947; de Morsier, 1960). Peterson and colleagues (1949) attribute the tremor which is thus caused in monkeys to the interruption, at the mesencephalic level, of inhibitory circuits descending from the central grey nuclei. Moreover Carrea and Mettler (1955) suggest that in this animal the damage to the ventral compound of the superior cerebellar peduncle constitutes the principle factor in producing the postural tremor, while Carpenter (1961) suggests the damage to the ascending cerebellofugal fibers before their arrival at the red nucleus. In contrast, Hassler and colleagues (1960) think that the destruction of these same fibers at the thalamic level is responsible for the suppression of the tremor in man. In our work, we have proposed that the postural tremor is the result of the concomitant damage to ascending nigral efferent nerves and to the corresponding rubrotegmentospinal passage (Poirier, 1960).

The hypokinesia which appears in the contralateral limbs following lesions involving this ventromedian tegmentary area, according to Carrea and Mettler (1955), would be a consequence of the simultaneous damage to the superior cerebellar peduncle and to the

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*Numbers in the margin indicate pagination in the foreign text.

substantia nigra. Orioli and Mettler (1957) and Carpenter (1957) have suggested that the concomitant damage to the rubrospinal passage aggravates the hypokinesia, results which we have confirmed in their entirety (Poirier, 1960; Poirier and colleagues, 1966).

In the light of studies by Hornykiewicz and colleagues (1960, 1962, 1964) who noted a considerable drop in the concentration of certain monoamines (in particular dopamine and serotonin) at the level of extrapyramidal structures in the brain in patients with Parkinson's disease, we studied the effect of pontomesencephalic lesions on the concentration of monoamines in the caudate nucleus and the putamen in monkeys and cats. In this way we demonstrated a direct relationship between cellular loss at the level of the locus niger (Poirier and Sourkes, 1964, 1965) and in the parabrachialis pigmentosus nucleus (Poirier and colleagues, 1967) on the same side as lesions involving the ventromedian tegmentum and a considerable drop in the level of dopamine in the corresponding striatum. We deduced from this the presence in the ventromedian tegmentum of nigrostriated dopaminergic pathways whose origin lies in the substantia nigra and the parabrachialis pigmentosus nucleus. /16

Also, Dahlström and Fuxe (1964) have shown, using the technique of histofluorescence, the presence of dopaminergic neurons in these structures.

Our findings (Poirier and Sourkes, 1965) enabled us to underline the importance of neurochemical disturbances resulting from damage to this nigrostriated pathway in the development of certain anomalies of motor function generally associated with syndromes which are called extrapyramidal.

A later study (Poirier and colleagues, 1966), based on more abundant material, allowed us to record some new findings. On the one hand we saw postural tremor develop after lesions which spared the rubrospinal pathway proper (which is magnocellular in origin), but which involved other fibers, extrarubral in origin, whose trajectory

is identical to that of the rubrospinal fibers. We concluded from this that the damage to the tegmentary compound in the rubro-tegmentospinal pathway is probably more significant in the development of tremor than that of the rubrospinal fibers proper. Moreover we confirmed, with monkeys showing symptoms of spontaneous tremor, that there is a destruction of the wholly ventromedian part of the tegmentum next to the interpeduncular space. Moreover, it is evident to us that the damage in this region is responsible for the considerable drop in serotonin which has been found in the ipsilateral striatum. Other studies have suggested that these serotoninergic fibers, ascending towards the caudate nucleus and the homolateral putamen, lead near the median line, and that they originate, at least in part, in neurons situated in the basomedian region of the pontomesencephalic tegmentum (Poirier and colleagues, 1967). Studies by Dahlström and Fuxe (1964) using the techniques of histofluorescence, demonstrate the presence of serotoninergic neurons in this region.

We have also shown that harmaline and harmine, which are reversible monoamine oxidase inhibitors, given the presence of certain tegmentary lesions, can induce postural tremor or greatly exaggerate spontaneous tremor for a period of about three hours (Poirier and colleagues, 1966; Sourkes and Poirier, 1966). It has also been established that harmaline disturbs dopamine metabolism (by reducing its concentration) and serotonin metabolism (by increasing its concentration at the level of cerebral structures) (Singh and colleagues, 1967; Poirier and colleagues, 1968).

In the light of these new facts we began this study with the aim of identifying more specifically the mechanisms involved in the genesis of postural tremor and hypokinesia and reconciling various hypotheses which seemed to us to conflict more in appearance than in reality.

Methodology /17

We used 34 monkeys (Macaca mulatta) of both sexes and varying in weight from 2 to 4 kilograms. Five monkeys (A, B, C, D, E) underwent

a lesion to the right side of the brain stem, the 29 others a lesion to the left side. Five of the latter underwent a second lesion involving the cerebral peduncle or the sensory motor cortex on the same side (see Table 1).

The brain stem lesions were caused by a high frequency current using a monopolar electrode previously implanted by stereotaxis. The animals were observed repeatedly: in their cages, in special chairs, or in a large cage equipped with a one-way window. All the animals were given harmaline (injected intramuscularly to a total dose of from 5 to 15 mg). Certain abnormal motor activities (tremor, athetosic movements, choreiforms, abnormal postures) were filmed or photographed. We also recorded the tremor mechanically (using a Grass transducer) or recorded the electromyographic activity in the muscles responsible for the tremor (using a cathode ray oscilloscope, Tektronix model 565 and a Grass model C4 camera).

The animals were killed by an overdose of Nembutal after 6 to 70 weeks (see Table I) and their brains were removed. In most cases, the caudate nucleus and putamen on each side were dissected and kept for chemical measurement and the brainstem and spinal column, and, in some cases, the entire brain were preserved in neutral formaldehyde at 10%.

The measurement techniques which we used were those of Bogdanski and colleagues (1956) for serotonin (5-hydroxytryptamine) and Sourkes and Murphy (1961) for dopamine and norepinephrine.

Certain pieces preserved in formaldehyde were treated with osmic acid using the method of Poirier, Ayotte and Gauthier (1964) before being coated and assembled in series sections. The other pieces were coated in paraffin and assembled in series sections before being colored using the technique of Klüver and Barrera (1953), except that we substituted basic fuchsin for cresil violet acetate.

Results

Neurological, Neurophysiological and Neuropharmacological Data (Table I)

Group A. Seven monkeys (BP9, BP24, BP26, BP43, BP44, BP45, BP68) having a ventromedian tegmentary lesion, in a postoperative period of from 10 to 70 weeks, showed symptoms of postural tremor in the two right limbs (Table I, group A). The tremor only affected the upper right limb in two other monkeys (BP50, BP72). On the other hand it occurred in a sporadic fashion in the lower right limb of BP45, in the upper right limb of BP68 and in the left limbs of BP26. This tremor, characterized by a rhythm of 4 to 7/s (Figure 1) and by its relative stability in any given animal, was most significant when the limbs were held in one given position and, in general, stopped outside of voluntary movements. An injection of harmaline (10 mg) caused a considerable increase in the incidence of episodes of tremor associated with a slight diminution in the rhythm which seemed to be linked to an increase in amplitude for a period of about 3 hours in all the animals of this group (Figure 1). Also this substance had the effect of inducing tremor in the lower right limb of BP50 and BP72 and in the left limbs of BP9. In contrast monkey BP26 reacted to a dose of 5 mg of harmaline by displaying, in the minutes which followed, a very intense tremor in all four limbs accompanied by increasing dyspnea to the point that we had to rapidly neutralize the effect by administering a small dose of pentobarbital. The tremor was associated with hypokinesia, hypotonia and, except for BP50, with atrophy of the right limbs. These animals held their upper right limb in triple semi-flexion only occasionally using it, and they showed a significant limpness in the lower right limb.

Monkey BP43 also showed, during a postoperative period of 60 weeks, some athetosic movements of the lower right limbs; these movements only appeared after some delay, that is about 4 minutes after the animal had been pushed and forced to move. They were preceded by a gradual extension of the limb which was no longer used. Once induced, they persisted for some time. At rest this monkey showed postural tremor in both right limbs.

TABLE I. NEUROLOGICAL AND NEUROPHARMACOLOGICAL RESULTS IN FOUR GROUPS OF MONKEYS HAVING RIGHT TEGMENTARY LESIONS (MONKEYS A, B,C,D,E) AND LEFT TEGMENTARY LESIONS (ALL THE OTHER MONKEYS)

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	Spontaneous tremor		Harmaline induced tremor		Hypokinesia		Survival period
	right	left	right	left	right	left	(weeks)
Group A							
BI'6	UL		UL	UL	UL		65(37)+
BI'24	UL		UL	UL	UL		43(18)
BI'26	UL	U.L.	UL	UL	UL		10
BI'43	UL		UL		UL		10
BI'44	UL		UL		UL		37(25)
BI'45	UL.		UL		UL		70(34)
BI'50	U .L		UL		UL		17
BI'68	U		UL		UL		15
BI'72			UL		UL		20
Group B							
BI'3	U.		UL				
BI'30	U .L.		UL				
BI'39	U .		UL	UL	UL		6
BI'40	U .L.	U.	UL		UL		44(33)
BI'71			UL	UL	UL		28
BI'78	L.		UL		UL		20
Group C							
BI'2			UL		U		
BI'5			U		U		
BI'8			U				6
BI'27			U				6
BI'31			UL		U		6
BI'65			UL		UL		10
BI'70			UL	U.L.	UL		17
BI'75			U				28
BI'80				U	UL		25
B				UL			23
D				UL			21
E				UL		UL	11
Group D							10
BI'7							9
BI'36							
BI'37							6
BI'49							16
BI'79							18
A							8
C							16
						L	10
						L	11

. Intermittant tremor
+ Number of weeks between first and second intervention
U Upper limb
L Lower limb

Group B. Six monkeys (Table I, group B) displayed sporadic /20
spontaneous tremor. This affected the upper right limb in 2 of them (BP3, BP64), the lower right limb in one other (BP78) the two right limbs in 2 others (BP39, BP66) and the lower left limb in the last (BP_{71}). An injection of harmaline had the effect of exaggerating the spontaneous tremor or of inducing tremor in the right limbs of BP3, BP39, BP66 and BP78 and in all four limbs in BP64 and BP71. The tremor was associated with hypokinesia, hypotonia and atrophy oi the right limbs in BP39 and BP66 and BP78 and with hypotonia in the lower right limb in BP64.

Group C. Twelve monkeys (Table I, group C) showed no postoperative spontaneous tremor. However, harmaline (10 mg) caused the appearance of tremor in the two contralateral limbs (Figure 1) in 10 of them, in the upper right limb in BP27 and in the two upper limbs in BP80. Also BP70 displayed tremor in both left limbs. In 7 monkeys of group C (BP2, BP3, BP51, BP65, BP70, BP80 and E) the lesion was associated with hypokinesia and, except in BP80, with hypotonia of the contralateral limbs.

Group D. Seven monkeys (Table I, group D) having unilateral lesions showed no tremor whether spontaneous or in response to harmaline. Two of them (A, C) displayed hypotonia of the contralateral limbs while 5 others displayed no detectable motor disturbance.

We should mention that we observed in several animals having various tegmentary lesions neurological symptoms other than those which were the principal object of this study. In fact several monkeys displayed oculomotor symptoms on the same side as the lesion through interruption of the corresponding nerve fibers. Some displayed cervical dystonia associated in some of them with dystonia of the trunk and/or with cerebellar ataxia following more extensive tegmentary lesions which involved as well as the structures listed above the ventral and lateral region of the substantia periaqueducalis on the pontomesencephalic level. Similarly we discovered in some of them a contralateral facial paralysis through damage to the corresponding

corticobulbar passage.

Neurochemical Data (Table II)

We determined the concentrations of serotonin and dopamine in the striatum (caudate nucleus and putamen) on both sides in most of the monkeys involved in this study. The results of these chemical measurements recorded in Table II provide evidence of an almost complete depletion in dopamine and serotonin in the striatum on the same side as the lesion in groups A and B although this is less evident for dopamine in group B. We also found a less significant drop in both monoamines in groups C and D. We will come back to these results after having described the lesions.

TABLE II. AVERAGE CONCENTRATIONS (μG/G) OF DOPAMINE AND SEROTONIN IN THE HOMOLATERAL AND CONTRALATERAL STRIATION IN FOUR GROUPS OF MONKEYS WITH TEGMENTARY LESIONS

Striatum	Dopamine		Serotonin		N.A.
	Homolateral	Contralateral	Homolateral	Contralateral	
Group A.....	0.2 (0.0-0.9)*	4.2 (2.3-5.9)	.01 (.00-.03)	.13 (.02-.22)	7
Group B.....	1.2 (0.0-4.4)	3.8 (2.3-4.7)	.00	.12 (.00-.20)	5
Group C.....	1.7 (0.0-5.5)	4.5 (1.9-6.7)	.10 (.00-.34)	.30 (.10-.64)	8
Group D.....	1.2 (0.0-3.9)	4.1 (3.2-5.1)	.24 (.13-.34)	.33 (.28-.38)	6

N.A. Number of animals
* Variation in individual values

Histopathological Data /21

General considerations: the majority of the monkeys used in these experiments had a relatively long postoperative survival period (see Table I). In consequence it was possible for us to test the damage to several nerve bundles not only by direct observation of the lesions themselves but also by referring on the one hand to the extreme paleness of the fibers at a distant point from the point of interruption and on the other hand to the cellular loss consequent on the retrograde

degeneration of the neurons in the nuclei of origin of the various bundles concerned. On the other hand, in several monkeys whose survival period was shorter we resorted to the technique of osmic acid impregnation (Poirier and colleagues, 1954) which allowed us to specify the trajectory and end point of other nervous pathways.

Thus the importance of the break in the crossed rubroefferent nerves (in the red magnocellular nucleus)and the direct rubroefferent nerves (in the parvocellular red nucleus) which are exclusively descending (Poirier and Bouvier, 1966) was determined through the intensity of the cellular loss at the level of the two divisions of the red nucleus consisting of entities which are clearly distinct in the monkey. The damage to the ascending cerebellofugal fibers was determined by studying the lesion and by the pallor of the fibers at a distant point from their interruption (Figure 6, 20, 30-32, 47, 51). The damage to the dopaminergic and serotoninergic fibers travelling towards the ipsilateral striatum was determined by the site of the lesion, the importance of the cellular loss at the level of the substantia nigra and of the parabrachialis pigmentosa nucleus (for dopamine) and of pontomesencephalic basomedian cellular groups (for serotonin) and by chemical changes in the ipsilateral striatum (Poirier and Sourkes, 1965a; Poirier and colleagues, 1966; Poirier and colleagues, 1967).

In the majority of the animals the unilateral lesion principally involves a region which stretches along the dorsomedian rim of the /22
substantia nigra from the upper part of the pons to the dorsal part of the mesencephalon (Figure 6-8. 16, 17). In some of them the lesion crosses the median line and results in bilateral damage to certain structures situated on both sides of it on a level with the pontomesencephalic ventromedian tegmentum (Figure 2, 13, 25, 41, 46). Also the lesion, which is generally strictly unilateral, interrupts fibers on the cross pathway on the level of the tegmentum and there follows a bilateral degeneration of ascending and oblique or descending bundles in some monkeys (Figure 15, 27, 28, 36, 39). Finally the destruction of the ventromedian and caudate part of the pontomesencephalic tegmentum is accompanied by a partial but significant cellular loss in the

nuclei dorsal to the raphe and the homolateral central upper nuclei (Figure 9, 29). Also we had to take account of the fact that the ventromedian tegmentary lesions cut a number of corticofugal fibers coming from the cerebral peduncle and travelling to various structure in the pontomesencephalic tegmentum.

In six monkeys (BP65 A, B, C, D, E) the lesion involves the dorsolateral part of the upper mesencephalic tegmentum (Figure 45) and in one of them (E) it extends into the ventromedian tegmentum.

The microscopic observation of monkey brains having lesions involving the pontomesencephalic tegmentum allowed us to identify four groups of descending fibers which originate in the red nuclei /23 and in the perirubral tegmentary substance. A first group of direct fibers made up of rubro-olivary fibers originating in the parvocellular red nucleus, by way of the central tegmentary tract (central bundle of the calotte), reaches the ventrolateral part of the corresponding principal olivary nucleus (Figure 38, 39, 41-44). A second group of descending and crossed fibers made up of axons which originate on the level of the red magnocellular nucleus switches with those of the opposite side borrowing the dorsocaudate part of the ventral tegmentary decussation (de Forel), going on to descend into the ventrolateral part of the brain stem at the opposite side to their place of origin. A third and very numerous group of axons proceeding from the extrarubral neurons travels into the rostral and ventrocaudate parts of the ventral tegmentary decussation before joining with the latter to form the compound rubrotegmentospinal bundle which descends into the lateral belt of the spinal column down to its most caudate segments (Figure 26-28). Finally, we were able to identify a fourth group of fibers situated lateral to the red nucleus in the mesencephalon. These fibers which we will henceforth call the "caudate efferent tegmentary bundle" have a ventromedial direction in the upper part of the projection, cross with those of the opposite side just below the pontic reticulotegmentary nuclei (possibly in Hatschek's decussation) going on to travel sideways towards the upper olivary nucleus where they seem to join the rubrotegmentospinal bundle (Figure 8, 10-12-41-44).

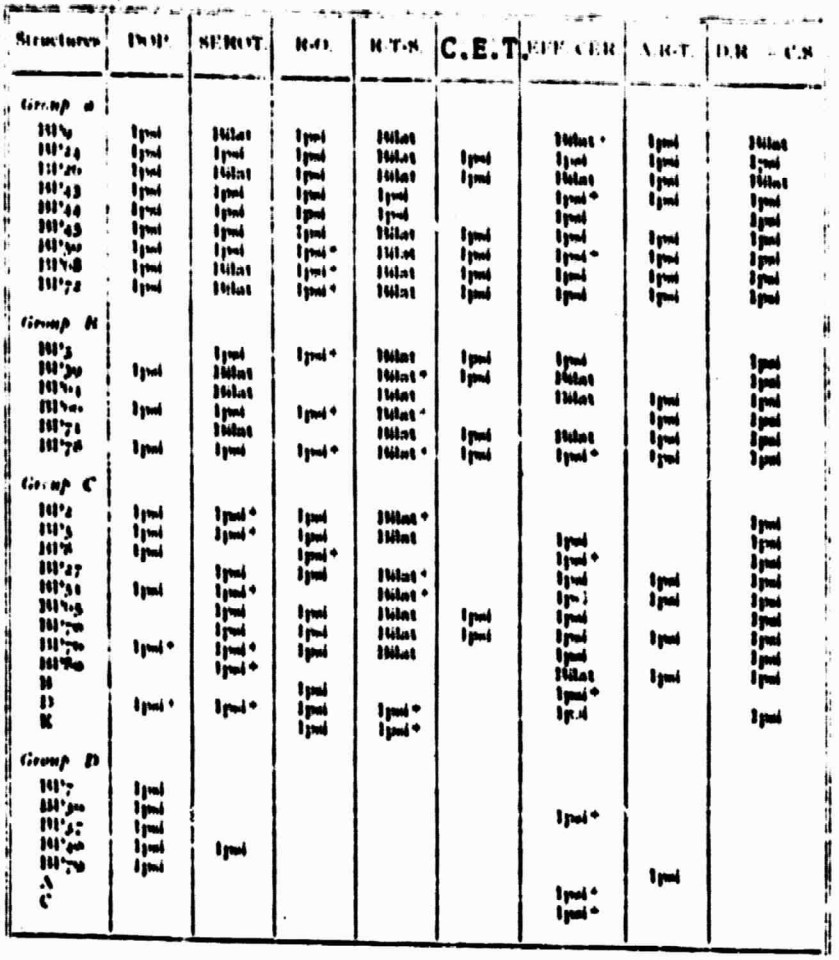
We also found a paleness on the level of the ipsilateral reticulo-tegmentary nucleus in several animals having ventromedian tegmentary lesions, a paleness which followed the interruption of a group of /24
descending fibers apparently coming from the homolateral cerebral peduncle. These fibers seem to correspond fairly well, from the point of view of their location, with the tegmentary temporopontic bundle as displayed on the level of the upper projection in Riley's atlas (1960).

Specific Aspects (Table III)

The neuroanatomical modifications caused by the lesions in the various groups of monkeys are summarized for the most part in Table III.

In the nine monkeys in group A the left ventromedian tegmentary lesion cuts extensively the ascending dopaminergic and serotoninergic pathways on the corresponding side, and the serotoninergic pathways are also interrupted on the right hand side in monkeys BP9, BP26, BP68 and BP72 where the lesion slightly crosses the median line (Figure 2, 6, 7, 13, 18, 19, 25). The rubro-olivary system is completely destroyed in six of the animals in this group, and the damage to this pathway is important but incomplete in BP50, BP68 and BP72 (Figure 3-5, 10-12, 14, 23, 24). On the other hand, the efferent nerves of the rubrotegmentospinal bundle sliced on the level /25
of their crossing-over points were cut bilaterally in seven animals and on the left side only (with respect to their point of origin) in the other two (BP43, BP44). The "caudate efferent tegmentary bundle" was cut before the crossing-over point in six monkeys of this group and was spared in BP9, BP43 and BP44 (Figure 2-5, 10-12, 22). The ascending cerebellofugal fibers were cut from the left hand side in all these monkeys and on both sides because of the paramedian destruction of Wernekink's decussation in BP9 and BP26. However we should add that one part of the cerebellothalamic portion of these pathways was spared in BP9, BP43 and BP50 (Figure 6, 7, 13, 16, 17, 19-21, 25). The afferent peduncular nerves of the left reticulo-tegmentary nucleus were destroyed in all the animals of this group with the exception of BP44. Certain nuclei of the median line and

TABLE III. PRINCIPLE NEUROANATOMICAL MODIFICATIONS IN FOUR GROUPS OF MONKEYS HAVING TEGMENTARY LESIONS WHETHER OR NOT ASSOCIATED WITH TREMOR AND HYPOKINESIS OF THE LIMBS



Structures	DOP.	SEROT.	R-O.	R-T-S.	C.E.T.	EFF. CER.	A.R.T.	D.R. + C.S.
Group A								
Group B								
Group C								
Group D								

DOP., dopaminergic; SEROT., serotoninergic; R-O., rubro-olivary; R-T-S., rubrotegmentospinal; C.E.T., caudate efferent tegmentary; EFF.CER., ascending cerebellofugal; A.R.T., afferent of the reticulotegmentary nucleus; D.R.+ C.S., nuclei dorsal to the raphe and upper central.

\+ significant but incomplete effect (see details in the text).

specifically the nuclei dorsal to the raphe and the central superior nuclei showed a significant cellular loss on the left hand side in all the monkeys and also on the right hand side in BP9 and BP26 (Figure 9). Finally, it should be noted that the lesion completely sliced the frontopontic pathway in BP26 and BP68 and the pyramidal system in BP26 (Figure 13-15).

The monkeys in group B also having a left ventromedial tegmentary lesion underwent a complete cut in the ascending serotoninergic pathways on the left side. These paths were also destroyed on the right hand side in BP39, BP64, BP71. The ascending dopaminergic pathways were extensively damaged on the left hand side in BP39, BP66, BP78 (Figure 26, 30, 33, 34).

The corresponding rubro-olivary system was significantly damaged in BP3, BP66 and BP78 and the rubrotegmentospinal bundle was destroyed /27
on both sides in all six animals (Figure 26, 28). However the magnocellular red nucleus on the same side as the lesion was only partly affected in BP39, BP66 and BP78 (Figure 33). The "caudate efferent tegmentary" bundle on the left hand side is absent following the cutting of its fibers above their crossing over point in BP3, BP39, BP71 and BP78. The ascending cerebellofugal efferent nerves were cut on both sides in BP39, BP64 and BP 71, on the left hand side in BP73 and BP78. They were spared for the most part in BP66 (Figure 26, 30-34). The peduncular efferent nerves travelling to the left reticulotegmentary nucleus were absent in BP64, BP66, BP71 and BP78 and intact in BP3 and BP39. The nuclei dorsal to the raphe and the left ventral upper nuclei displayed a significant cellular degeneration in all the animals in group B (Figure 29). Finally the left frontopontic fibers were destroyed in BP39.

As shown in Table III the monkeys in group C underwent a more or less significant cut in the ascending monoaminergic pathways on the same side as the lesion. Moreover ten of the twelve animals in this /28
group displayed a significant effect on the ipsilateral rubro-olivary system which was spared only in BP51 and BP80 (Figure 35-39, 41-44, 51). The rubrotegmentospinal pathway was cut on both sides in seven monkeys

(BP2, BP5, BP27, BP51, BP65, BP70 and BP76), ipsilaterally in two (G, E), and spared in the other three (BP8, BP80, B). However the magnocellular red nucleus which provides a share of fibers to this pathway was only partially affected in BP2, BP27, BP51, D, E (Figure 35-41, 47-50). The "caudate efferent tegmentary bundle on the same side as the lesion was interrupted only in BP55 and BP70 (Figure 41-55). The cerebellar efferent nerves travelling in the ascending branch of the brachium conjunctivum were sliced on the same side as the lesions in nine monkeys (BP5, BP8, BP27, BP51, BP65, BP70, BP76, B, D) and on both sides in BP80. Nevertheless, this degeneration, partial in two of them (BP8, B) principally involves the cerebello-thalamic component of this pathway while in another (BP70) we noted a very partial degeneration of the fibers on the right hand side. This pathway was not damaged in BP2 and E (Figure 34, 38, 41, 45-51). The peduncular efferent nerves on a level with the left reticulotegmentary nucleus were missing in BP27, BP51, BP70 and BP80. The nuclei dorsal to the raphe of the left central upper nuclei displayed a cellular degeneration in all the animals of group C except B and E. Finally the lesions cut the left frontopontic fibers in BP76 and BP80 and left median leminiscus in BP65, B and E (Figure 45, 46).

Five of the seven monkeys in group B displayed a significant cut in the left ascending dopaminergic pathways associated in one of them (BP40) with the destruction of the corresponding serotoninergic pathway (Figure 52, 53). Further, the rubral and descending and crossing tegmentary efferent nerves were not destroyed in any of the monkeys in this group and only monkey BP79 shows an absence of peduncular efferent nerves on the level of the left reticulotegmentary nucleus. In three of the monkeys in this group (BP36, A and C) only the cerebello-thalamic portion of the ipsilateral ascending branch of the brachium conjunctivum degenerated following a lesion which caused a cut in these fibers on the level of the part dorsal to the parvocellular red nucleus or higher (Figure 52).

Correlation of Data (Tables I, II, III)

Comparing the neuroanatomical modifications, the neurochemical changes and the neuropharmacological effects of harmaline on the one

hand and the neurological disturbances on the other has enabled us to confirm the following facts.

The complete interruption, by itself or with other factors, of the dopaminergic and ascending cerebellofugal pathways (BP5, BP51) associated with the interruption of the corresponding rubrotegmentospinal fibers (BP5) is not associated with spontaneous tremor. Further damage, whether by itself or with other factors, to the serotoninergic pathways, the ascending cerebellofugal pathways and the corresponding rubrotegmentospinal pathways (BP9, BP64, BP71, contralateral to the lesion and BP65, BP70 ipsilateral) associated with the destruction of the rubro-olivary pathways and "caudate efferent tegmentary" pathways and with the degeneration of the upper central nuclei and the nuclei dorsal to the raphe (BP65, BP70) does not cause spontaneous postural tremor (Tables I, II, III, group C, D). /30

Spontaneous postural tremor only occurs in any sustained way in the presence of lesions which simultaneously involve the dopaminergic and serotoninergic ascending pathways and the corresponding cerebellofugal rubrotegmentospinal and rubro-olivary systems and which also involve the nuclei dorsal to the raphe and upper central on the same side (Tables I, II, III, group A). It is important to remember that in these circumstances the concomicant interruption in the peduncular efferent nerves on the reticulotegmentary level, in the caudate efferent tegmentary bundle, and even in the corresponding corticospinal and frontopontic pathways (group A) does not prevent the appearance of sustained spontaneous tremor.

Also we observed the development of postural tremor which only appeared in a sporadic fashion following similar lesions which, however, did not damage the corresponding rubro-olivary dopaminergic or cerebellofugal pathways (Table I, II, III, group B).

Harmaline does not induce tremor in the presence of damage, either isolated or concomitant, to the dopaminergic and serotoninergic pathways (group D) or the corresponding serotoninergic and rubrotegmentospinal pathways (Table III, right side in monkeys BP68 and BP72 of

group A) or the corresponding dopaminergic and cerebellothalamic pathways (Table III, group D). /31 However, harmaline caused tremor in monkeys having lesions which destroyed the rubro-olivary bundle or the collection of ascending cerebellar efferent nerves with or without concomitant damage to the rubrotegmentospinal system and the corresponding monoaminergic mechanisms (Tables I, II, III, groups A, B, C).

Several monkeys displayed a significant motor deficiency characterized by hypokinesia and hypotonia whether associated or not with atrophy in the corresponding muscular masses in the contralateral limbs. These disturbances appeared following lesions which simultaneously affected the dopaminergic, serotoninergic and ascending cerebellofugal pathways and the corresponding tegmentary and rubral efferent nerves with or without concomitant damage to other structures. By way of example we would mention all the monkeys in group A and monkeys BP39, BP66 and BP78 in group B (Tables I, II, III). Further, /33 monkeys BP3, BP64, BP71 in group B, having lesions affecting numerous nervous pathways but excluding the dopaminergic pathways, displayed only slight motor deficiency other than tremor. In general we confirmed that hypokinesia and/or hypotonia were less significant in the animals in group C except BP51 and BP65. In these two, hypokinesia appeared following the interruption of the serotoninergic and ascending cerebellofugal pathways in the rubrotegmentospinal system and in the corresponding nigrostriated (BP51) or striatonigral (BP65) pathway.

Effect of Concomitant or Secondary Lesions of the "Pyramidal" System

In one monkey (BP26) having a ventromedian tegmentary lesion encroaching on the left cerebral peduncle the frontopontic and corticospinal fibers were completely cut (Figure 13-15). By contrast monkey BP45, having a left ventromedian tegmentary lesion, 47 weeks after the first intervention underwent a second left hand lesion which destroyed the corticospinal pathway (Figure 24). This concomitant or secondary cut in the corticospinal pathway neither prevented nor suppressed the appearance of spontaneous postural tremor any more

than it prevented or suppressed tremor induced by harmaline in two monkeys. In contrast four monkeys (BP9, BP24, BP39, BP44) which had displayed spontaneous tremor following tegmentary lesions (see Table I) underwent homolateral cortical lesions after an observation period of from 16 to 37 weeks. This damage involving the apex of the precentral and postcentral surfaces in BP24 and the base in BP39 suppressed the tremor, whether spontaneous or induced by harmaline, in the corresponding contralateral limb during survival periods of 43 and 23 weeks respectively. In contrast a destruction involving the apex of the precentral surface (BP9) or postcentral surface (BP39) and the apex and the base of the postcentral surface (BP44) led in three monkeys to a suppression of spontaneous tremor in corresponding contralateral limbs without, however, abolishing the response to harmaline in the same limbs.

Commentary

This study has confirmed that the destruction of monoaminergic pathways together with the interruption of other nervous pathways leading to the level of the ventromedian tegmentum can cause postural tremor and/or hypokinesia which will be more or less significant in contralateral limbs (Poirier and colleagues, 1966). On the other hand harmaline has proved itself effective in inducing tremor in monkeys having lesions which in this case do not damage the /34 corresponding monoaminergic efferent nerves of the striatum. However the potentializing effect of this drug on spontaneous tremor can be seen to its fullest extent only in monkeys whose striatum contains no effective quantities of dopamine and serotonin. This study also makes evident that harmaline cannot induce tremor in the presence of lesions which entail an isolated cut in the monoaminergic afferent nerves of the striatum. These results underline the importance of a simultaneous approach to the monoaminergic mechanisms and the non-monoaminergic neuronal circuits in the genesis of tremor and other disturbances of motor acitvity.

Thanks to some experimental material contained in the brains where the lesions were more varied and the degeneration of certain

nervous pathways more evident by reason of the long survival period of the animals we were able this time to extract more morphological information.

These results confirm that the ventromedian tegmentary region corresponding to the surface of Tsaï, contains ascending pathways whose interruption results in a retrograde degeneration of the neurons of the substantia nigra of the parabrachialis pigmentosis nucleus and of basomedian cellular groups at the pontomesencephalic level on the same side as the lesions. These morphological changes are associated with a considerable drop in the level of dopamine and serotonin in the ipsilateral striatum (Poirier and colleagues, 1965, 1966, 1967). These monoaminergic pathways link the brain stem to the striatum (Anden and colleagues, 1964; Fuxe and colleagues, 1964) and appear to be essential to the synthesis of dopamine and serotonin in the striatum since their interruption prevents the formation of dopamine and serotonin from their immediate precursors, L-DOPA and 5-hydroxytryptophane (Poirier and colleagues, 1967). Moreover it seems that these pathways control the synthesis of these two amines from remote precursors considering that their suppression is accompanied by a considerable diminution of hydroxylases of tyrosine (Goldstein and colleagues, 1966; Poirier and colleagues, 1969) and tryptophan (Poirier and colleagues, 1969) on the level of the striatum on the same side as the tegmentary lesions. These last facts suggest the possibility that the monoaminergic pathways may be the seat of enzymatic mechanisms which are involved in the synthesis of these amines. Also Olivier and colleagues (1968) have reported that the strionigral fibers are the seat of intense cholinesterasic activity which disappears after striatial lesion. These latter pathways seemed to form part of a strionigrostriate loop thanks to which the striatum controls its own needs for dopamine by direct action on the dopaminergic neurons contained in the corresponding substantia nigra and parabrachialis pigmentosis nucleus.

As we mentioned earlier lesions involving the ventromedian tegmentary region cause a significant retrograde degeneration in the nuclei dorsal to the raphe and the central superior nuclei on the same side. The neurons in these nuclei are strongly serotoninergic

[as observed with the aid of histofluorescence (Dahlström and Fuxe, 1964)]. This ventromedian tegmentary region then contains not only the many neurons which are the origin of the ascending monoaminergic pathways ending in the diencephalon and telencephalon, but also it seems that many serotoninergic fibers end there. The evidence of an abnormally high concentration of serotonin at the mesencephalic level (Bernheimer and colleagues, 1961; Maickel and colleagues, 1968) supports such an assertion. So it is not impossible that the disturbance of the serotoninergic mechanisms in the pontomesencephalic region contributes to the appearance and maintenance of spontaneous postural tremor.

Following lesions involving the ventromedian tegmentum on /35
the pontomesencephalic level we were able to specify that the rubrotegmentospinal bundle coming out of the ventral tegmentary decussation carries fibers which originate not only in the magnocellular red nucleus but also in the surrounding tegmentary substantia (Poirier and Bouvier, 1966). Very often unilateral lesions on this level are associated with a bilateral interruption of this pathway caused by the paramedian damage to Forel's decussation. Another pathway, also crossing and descending, which we have called the "caudate efferent tegmentary bundle" is often involved in monkeys displaying tremor and other motor deficiencies in contralateral limbs. These three groups of pontomesencephalic fibers finish at the level of contralateral structures situated more caudally. Together they represent an important component of fibers capable of acting directly or indirectly on the peripheral motor neurons. Also the cellular groups which give birth to the descending crossing pathways receive numerous afferent nerves from the sensory motor cortex (Kuypers and Lawrence, 1967), from the extrapyramidal system through the pallidomesencephalic bundle (Nauta and Mehler, 1966) and from the cerebellum through cerebellotegmentary fibers and cerebellorubral fibers from the upper cerebellar peduncle. The tegmentary lesions associated with various motor disturbances in contralateral limbs destroy other pathways which are in indirect relation with the tegmentary and rubral efferent nerves mentioned above. Indeed they frequently involve an interruption in the corticofugal fibers

finishing in the ipsilateral reticulotegmentary nucleus and in the rubro-olivary fibers which connect the red parvocellular nucleus to the corresponding bulbar olive. And these two structures, the reticulotegmentary nucleus and the principle olivary nucleus, are related to the contralateral part of the cerebellum through crossed fibers. In turn the cerebellum, thanks to efferent nerves of fastigiate origin travelling to the bulb and to efferent nerves coming from other cerebellar nuclei travelling to the pontomesencephalic tegmentum, is capable of acting at these two levels under the influence of numerous afferent nerves including those of the corresponding reticulotegmentary nucleus and the rubro-olivary system.

It emerges from the analysis of the results of this study that the principal neuronal circuit involved in the genesis of harmaline induced tremor corresponds to the rubro-olivocerebellorubral loop consisting of the parvocelluar red nucleus, the bulbar olive, the cortex and the nuclei of the cerebellum. In the monkey this multisynaptic circuit involves a network in the parvovellular red nucleus (Poirier and Bouvier, 1966). So it would differ from the triangle of Guillain and Mollaret (1931) involved in the appearance of myoclonus in man, because of the absence of dento-olivary fibers (Trelles, 1943). This neuronal circuit, itself subject to cortical influences notably on the level of the parvocellular red nucleus (Kuypers and Lawrence, 1967), is capable of influencing the following three different levels through cerebellofugal efferent nerves: the intralaminary nuclei and the lateral and anterior regions of the thalamus, the rubral and crossed efferent tegmentary systems originating in the pontomesencephalon, and the reticulospinal system which is bulbar in origin. Further this neuronal circuit made up of the parvocellular red nucleus, the ventrolateral part of the bulbar olive and the cerebellum and its efferent nerves is unique to primates which until now are the only animals reported to have had Parkinsonian type tremors. We hope that thanks to harmaline which apparently lets us achieve a selective pharmacological interruption in the monoaminergic mechanisms, we will now be able to proceed with more limited lesions and thus detect more precisely the nonmonoaminergic neuronal mechanisms involved in the appearance of spontaneous postural tremor.

The appearance of spontaneous tremor despite the complete interruption (on the level of the cerebral peduncle) of the corresponding corticospinal pathways demonstrated in ten monkeys confirms our prior observations (Poirier and colleagues, 1965, 1966, 1967). On the other hand, the permanent suppression of spontaneous tremor and even of tremor induced by harmaline through lesions involving the corresponding sensory motor cortex allows us to draw certain preliminary conclusions. The destruction of the sensory motor cortex entails only a very partial degeneration in the corticofugal fibers travelling on the level of the cerebral peduncle and the bulbar pyramid and would thus be more effective in abolishing tremor than the complete interruption of the corticospinal pathways at the peduncular level. Consequently the integrity of the "extra peduncular" corticofugal pathways seems more essential in postural tremor than the frontopontic and corticospinal bundles. However we should not for the meantime exclude the possibility that the causal lesion might play a determining role in the greater or lesser resistance of tremor to the suppression of neuronal circuits originating in higher centers.

Further it is possible that the interruption of these circuits is generally sufficient to suppress tremor in the presence of partially disturbed antagonistic mechanisms. The region of the ventrolateral nucleus of the thalamus whose destruction effectively abolishes rigidity and tremor in Parkinson's disease (Cooper, 1965, Selby, 1967) contains nervous structures which play a part in the transmission of rhythmic influxes according to electrophysiological studies in man (Guiot, Hardy and Albe-Fessard, 1952; Jasper and Bertrand, 1966) and in monkeys with tremor (Cordeau and colleagues, 1960; Lamarre and Cordeau, 1967). It is noteworthy that this area of the thalamus, a network in a corticothalamocortical loop involving the precentral motor surface receives numerous cerebellar and pallidal afferent nerves while the adjacent thalamus receives the median lemniscus. Interrupting the cerebellothalamic afferent nerves and the median lemniscus does not prevent the appearance of postural tremor in monkeys; on the contrary it probably exaggerates it. On the other hand the destruction of the pallidum may, it seems, abolish tremor in man, suggesting

that the pallidofugal fibers have some sort of role to play in releasing tremogenic influxes. The pallidum moreover is almost exclusively under the control of the striatum which is the site of important monoaminergic and cholinergic mechanisms as mentioned above. The preponderance of cholinergic activity associated with a considerable reduction in striatial monoaminergic activity in Parkinson's disease once again underlines the importance of the the striopallidum and its efferent nerves in the control of motor activity.

The ventromedian tegmentary lesions described above were accompanied in several monkeys by severe hypokinesia of the contralateral limbs which was particularly apparent on the level of the upper limbs. This, frequently linked with hypotonia and muscular atrophy, was characterized by the fact that the animal only used its limb infrequently and generally held it in triple semi-flexion.

This hypokinesia occurred after lesions which simultaneously involved the ascending monoaminergic pathways in certain of the descending and crossing efferent nerves of rubral and perirubral origin and/or the cerebellofugal and corticofugal afferent nerves /31 which finish in this pontomesencephalic region. Walker and Richter (1966) were struck by the seriousness of hypokinesia after the complete slicing of the cerebral peduncle which however was associated with a softening of the locus niger in the monkeys. In is interesting to link these results with the observations of Lawrence and Kuypers (1968) who confirmed the appearance of a deep and sustained hypokinesia particularly evident on the level of the ipsilateral upper limb in the monkey, only after lesions involving both the two bulbar pyramids and the lateral part of the bulb on one side. On the other hand either of these two lesions alone does not result in any significant hypokinesia which led these authors to conclude that hypokinesia results from the combined interruption of the corresponding corticospinal and rubrospinal pathways. In the light of the results of this study it seems to us that on the morphologic plane the bulbar and lateral pontic lesions reported by these authors cut not only the rubrospinal pathways but also numerous other crossed fibers of extrarubral orogin. Further on the functional plane it is interesting

to confirm that lesions involving the rubral and ascending efferent tegmentary system in association in one case with the corresponding pyramidal system (Lawrence and Kuypers, 1968) and in the other case with corresponding striatial and thalamic afferent nerves (as demonstrated in this study) display a similar motor deficiency. The fact that in our experiments the break in the efferent tegmentary and rubral system above its crossing over point caused hypokinesia in the contralateral limbs added to the above mentioned observations of Lawrence and Kuypers (1968) and other researchers (Orioli and Mettler, 1957; Carpenter, 1957; Poirier, 1960) underlines the importance of not only rubral efferent nerves but also perirubral nerves in the control of spontaneous locomotor activity. However these neurons which are themselves under the influence of cerebellar afferent nerves of the sensory motor and pallidal afferent nerves are apparently not essential to normal locomotor activity since the interruption of their axons alone does not result in any noticeable motor deficiency, at least in monkeys (Poirier and Bouvier, 1966). As mentioned above, it seems further that the interruption of striatal and thalamic afferent nerves may be substituted for that of the corresponding pyramidal pathway in producing hypokinesia. This suggests that the suppression of these afferent nerves which in fact directly or indirectly deprives the lateral and anterior thalamus and consequently the sensory motor cortex of important influences could contribute to the production of hypokinesia by cutting off the essential input from the pyramidal system.

The appearance of athetosic movements which has been shown in an animal after a ventromedian tegmentary lesion cannot be linked to any particular pathological change other than those simultaneously responsible for the tremor and the hypokinesia which have been noticed in that animal. However the appearance after some delay (after about 4 minutes) of these movements in response to prompting leads us to believe that specific neruochemical disturbances coincide with their appearance.

Summary /38

Thirty four monkeys having various tegmentary lesions on the

level of the pontomesencephalon whether or not displaying spontaneous tremor, tremor induced by harmaline and/or hypokinesia in the contralateral limbs were used in a study of neuroanatomical, neurochemical, neurological and neuropharmacological correlations.

The results of this study have emphasized the importance of the monoaminergic mechanisms of the brain stem and particularly of those which lead to the striatum, in extrapyramidal functioning. They also show the importance of the crossed descending tegmentary rubral system (magnocellular in origin) and of the rubro- (parvocellular in origin) olivocerebellar circuit and its efferent nerves in controlling peripheral motor activity.

The simultaneous interruption of these various neurocircuits (monoaminergic and other) is accompanied by sustained tremor as in Parkinson's disease and/or hypokinesia in the contralateral limbs. On the other hand, harmaline, a reversible monoamine oxidase inhibitor, is capable of inducing tremor in the presence of lesions which do not damage the ascending monoaminergic pathways of the brain stem.

The destruction of the sensory motor cortex proves a more effective way of abolishing spontaneous tremor or harmaline induced tremor than the complete interruption of the pyramidal system on the level of the cerebral peduncle.

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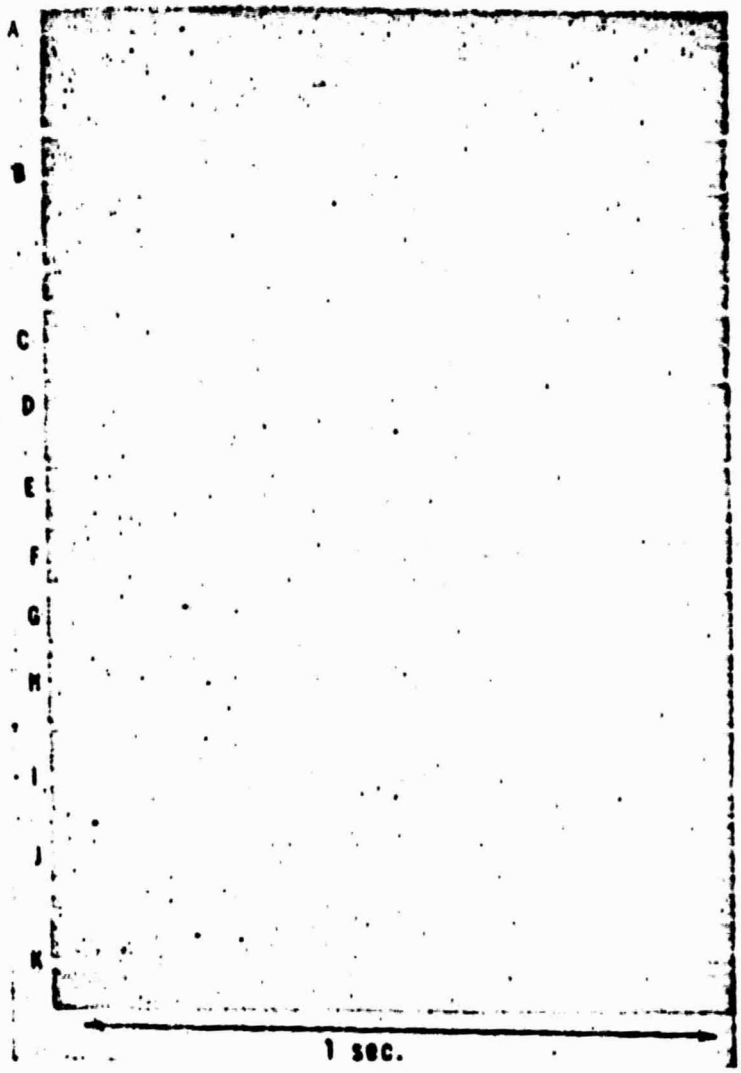

Figure 1. Examples of electromyographic curves in monkeys having left tegmentary lesions. Monkey BP9 brachioradial muscles (above) and sural triceps (below) on the right, spontaneous tremor (A); effect of harmaline (B); after left cortical lesion, right biceps, spontaneous tremor (C), effect of harmaline (D). Monkey BP24, right deltoid, spontaneous tremor (E), effect of harmaline (F); after left cortical lesion, right deltoid, spontaneous tremor (G), effect of harmaline (H). Monkey BP45, right biceps, spontaneous tremor (I). Right quadriceps, effect of harmaline (J). Monkey BP50, right deltoid, effect of harmaline (K).

Figure 2. BP9 transverse cuts to the mesencephalon. Left lesion having slightly crossed median line. (Color. Klüver modif. Gr. x 6.)

Figure 3-5. BP9. Transverse cuts to the upper pons showing the absence of ipsilateral rubro-olivary fibers (ro) and the presence of the caudate efferent tegmentary bundle (cet) on both sides. (Color. Klüver. modif. Gr. x 10, x 40, x 40, resp.)

Figure 6-8. BP24. Transverse cuts at three ponto-mesencephalic levels illustrating a left lesion which has destroyed the parvocellular and magnocellular subdivisions of the red nucleus and the left ascending cerebellofugal branch. Also note the disappearance of the ipsilateral substantia niger neurons and the interruption in the afferent nerves of the reticulotegmentary nucleus and the caudate efferent tegmentary bundle (cet) before its crossing. (Color. Klüver modif. Gr. x 6, x 6, x 8, resp.)

Figure 9. BP24. Transverse cut in the upper pons. Partial degeneration of the nucleus dorsal to the ipsilateral raphe. (Color. Klüver modif. Gr. x 40.)

Figure 10-12. BP24. Transverse cuts to the upper pons showing the absence of ipsilateral rubro-olivary fibers (ro) and of the contralateral caudate tegmentary bundle (tec) (beneath its crossing). (Color. Klüver modif. Gr. x 10, x 40, x 40, resp.)

Figure 13. BP26. Transverse pontomesencephalic cut. Left lesion which has crossed the median line. This has caused a complete interruption in the corticopontic and corticospinal bundles on the left and the disappearance of the corresponding neurons of the substantia nigra. This lesion also interrupted the rubrotegmentospinal bundles and the ascending cerebellofugal efferent nerves on both sides. (Color. Klüver modif. Gr. x 6.)

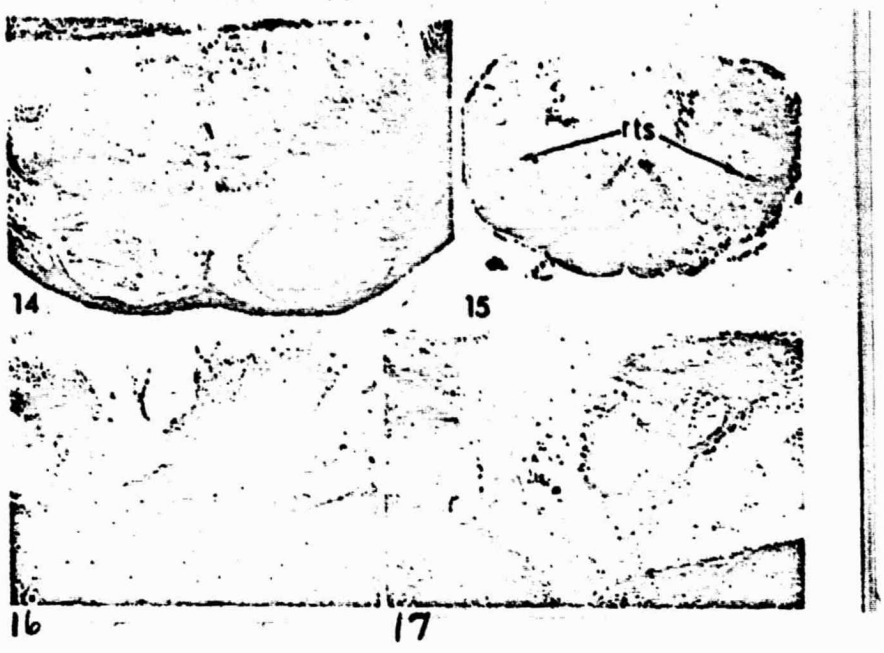

Figure 14. BP26. Transverse cuts at the level of the pons showing the diffuse degeneration of the rubro-olivary and ipsilateral corticofugal fibers (survival period only 10 weeks). (Color. Klüver modif. Gr. x 10.)

Figure 15. BP26. Transverse cut to the middle bulb (in the same monkey) illustrating the degeneration of the ipsilateral corticospinal fibers and both rubrotegmentospinal pathways. (Color. Osmic acid. Gr. x 8.)

Figure 16-17. BP43. Transverse pontomesencephalic cuts showing a left lesion which destroyed the magnocellular and parvocellular subdivisions of the left red nucleus and the ascending cerebellofugal branch on the same side. This lesion also caused the disappearance of the neurons of the substantia nigra on the left side and reached the corresponding rubrotegmentospinal pathway. (Color. Klüver modif. Gr. x 8 resp.)

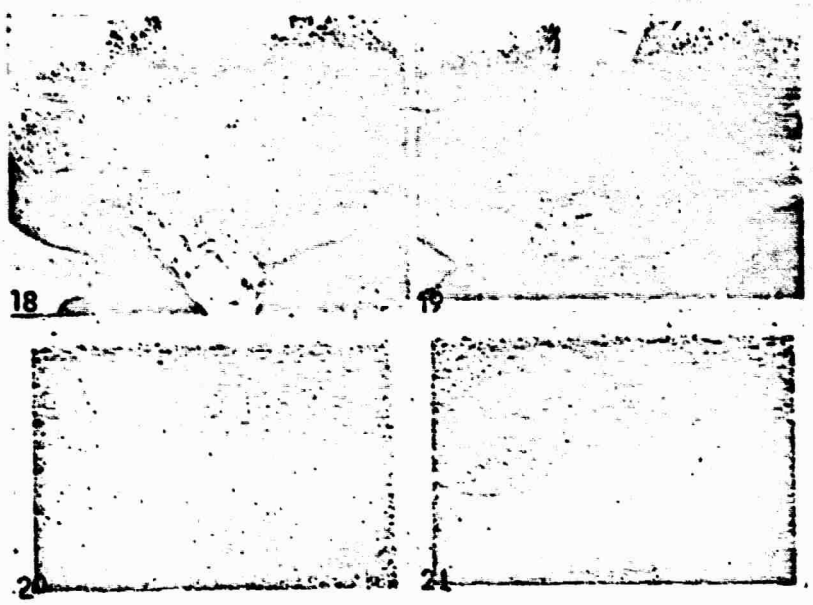

Figure 18-19. BP45. Transverse cuts to the mesencephalon showing the left lesion which has destroyed the dopaminergic and serotoninergic afferent nerves of the ipsilateral striatum and the corresponding ascending cerobellofugal efferent nerves. This lesion also interrupted the ipsilateral rubro-olivary and caudate efferent tegmentary bundles and the two rubrotegmentospinal bundles. (Color. Klüver modif. Gr. x 6, resp.)

Figure 20-21. BP45. Transverse cuts to the thalamus illustrating the absence of cerebellothalamic afferent nerves on the level of the left ventrolateral nucleus (Figure 20) and their presence on the right (Figure 21). (Color. Klüver modif. Gr. x 40, resp.)

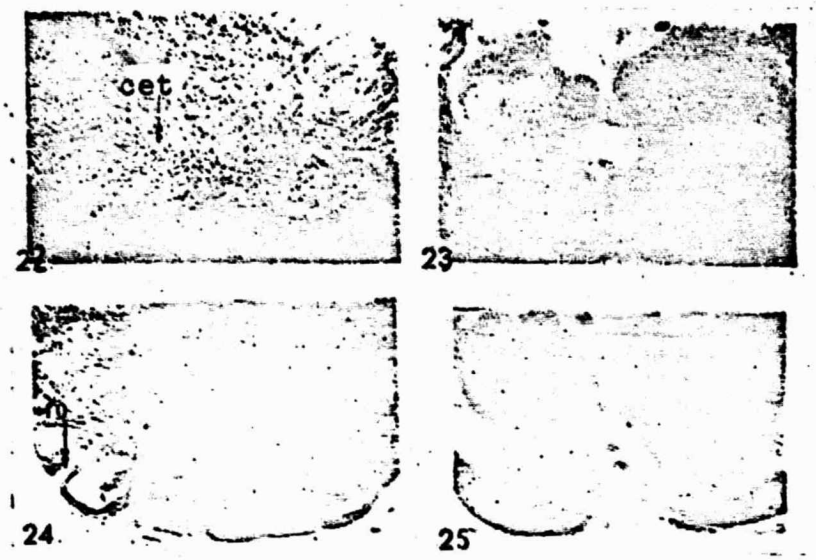

Figure 22. BP45. Transverse cut on the left side of the pons showing the caudate efferent tegmentary (cet) bundle on the right side (below its crossing). (Color. Klüver modif. Gr. x 40.)

Figure 23. BP45. Transverse cut on the level of the pons showing the absence of the left rubro-olivary bundle (ro). (Color. Klüver modif. Gr. x 25.)

Figure 24. BP45. Transverse cuts to the upper bulb showing the paleness at the level of the left bulbar olive resulting from the degeneration of the corresponding rubro-olivary fibers (ro). The atrophy and paleness of the left bulbar pyramid are the result of a second intervention in this animal. (Color. Klüver modif. Gr. x 6).

Figure 25. BP72. Transverse cut to the mesencephalon showing a left ventromedian tegmentary lesion which has crossed the median line. This has cut the ipsilateral serotoninergic and dopaminergic fibers on both sides. It has also caused an interruption in the ascending cerebellofugal efferent nerves and in the rubro-olivary fibers on the corresponding side as well as causing degeneration in the corresponding caudate efferent tegmentary bundle and the two rubrotegmentospinal pathways. (Color. Klüver modif. Gr. x 6.)

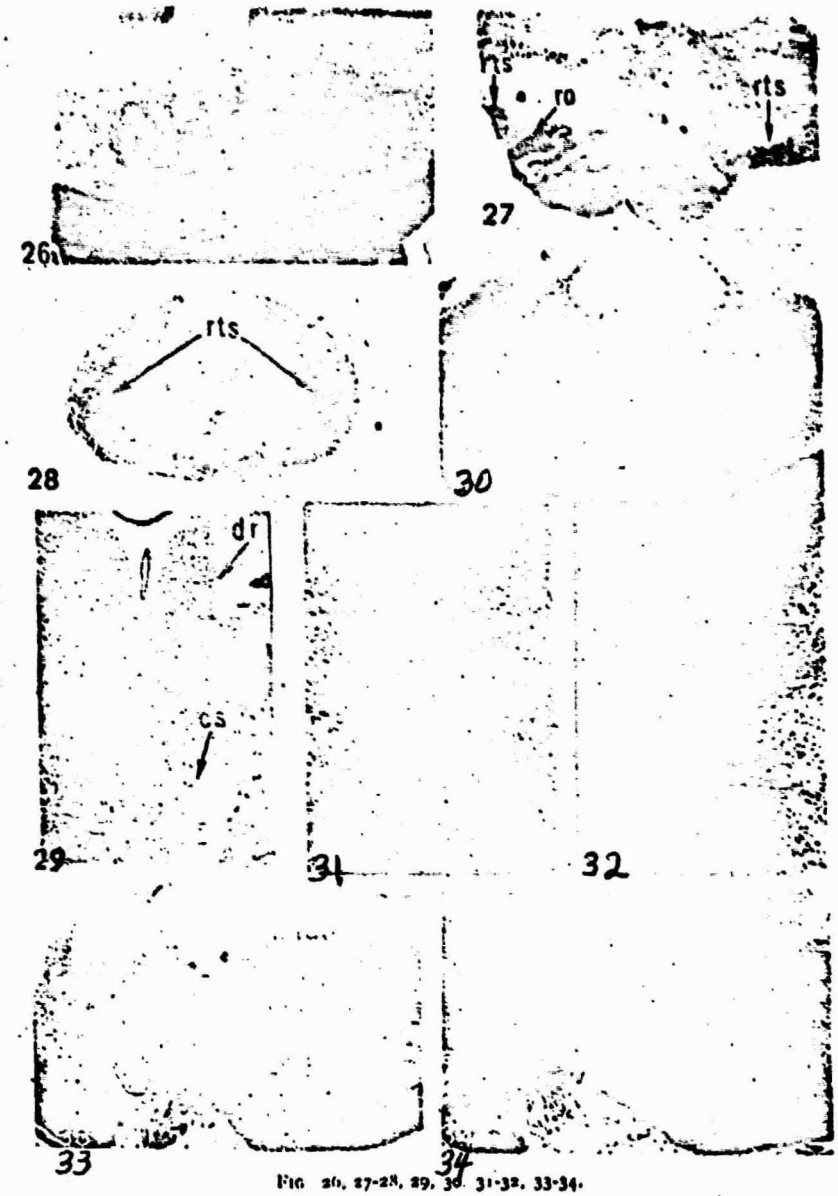

Fig. 26, 27-28, 29, 30, 31-32, 33-34.

[Captions for these Figures on following page]

Figure 26. BP3. Transverse cut to the mesencephalon showing a left lesion reaching the red nucleus and the corresponding ascending cerebellofugal fibers. (Color. Klüver modif. Gr. x 8.) /28

Figure 27-28. BP3. Transverse cuts to the bulb and spinal column showing the degeneration of the rubro-olivary fibers (ro) on the same side and the rubrotegmentospinal pathways (rts) on both sides. (Color. Osmic acid. Gr. x 10, resp.)

Figure 29. BP3. Transverse cut to the upper pons illustrating the retrograde degeneration of the neurons of the nuclei dorsal to the raphe (dr) and central superior (cs) on the same side. (Color. Klüver modif. Gr. x 40.)

Figure 30. BP64. Transverse cuts to the mesencephalon showing a left lesion which crosses the median line of this level. Note that this lesion has cut the serotoninergic fibers on both sides but has not damaged the dopaminergic fibers. (Color. Klüver modif. Gr. x 6.)

Figure 31-32. BP64. Transverse cuts to the mesencephalon illustrating the parvocellular red nucleus (rp) and the substantia nigra (sn) which are saved on both sides. On the other hand the abnormal paleness of the parvocellular red nuclei is due to the extent of degeneration of the ascending cerebellar efferent nerves on both sides. (Color. Klüver modif. Gr. x 40, resp.)

Figure 33-34. BP66 and BP 78. Transverse cuts to the mesencephalon. Ventromedian tegmentary lesion having cut the dopaminergic and serotoninergic fibers on their way to the ipsilateral striatum and an important part of the rubro-olivary fibers. (Color. Klüver modif. Gr. x 8, resp.)

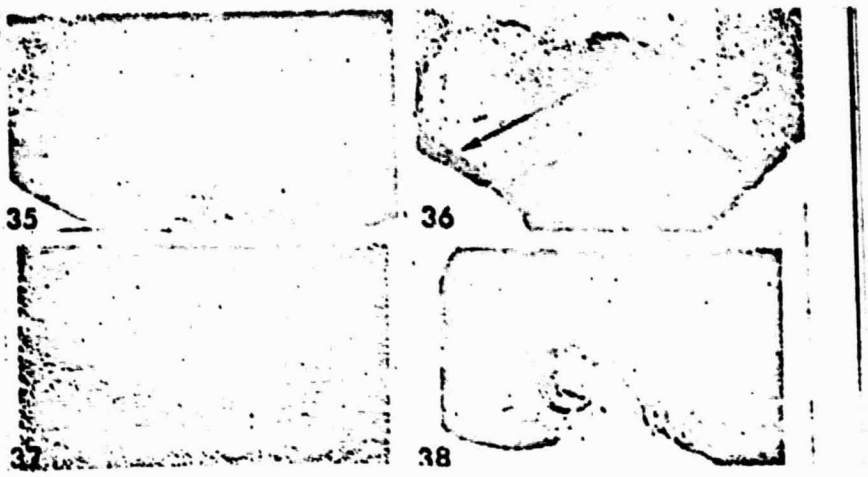

Figure 35. BP2. Transverse cut to the mesencephalon. Left ventromedian tegmentary lesion have destroyed the lower part of the ventral tegmentary decussation. This monkey was also subjected to a small left lesion affecting the corresponding central tegmentary bundle on the level of the upper projection. (Color. Klüver modif. Gr. x 8).

Figure 36. BP2. Transverse cuts to the superior bulb. Degeneration of the tegmentary component of the two rubrotegmentospinal bundles (rts) resulting from the rostral and paramedian damage to the ventral tegmentary decussation. Note also the degeneration in the left rubro-olivary fibers (ro). (Color. Osmic acid. Gr. x 8).

Figure 37. BP2. Left magnocellular red nucleus. The two magnocellular red nuclei do not display retrograde degeneration in this animal because the lesion spared the most caudate fibers of the ventral tegmentary decussation. (Color. Klüver modif. Gr. x 100.)

Figure 38. BP5. Transverse cuts to the mesencephalon. Left ventromedian tegmentary lesion involving the substantia nigra, the red nucleus and the ascending cerebellofugal efferent nerves on the same sides as the lesion. (Color. Klüver modif. Gr. x 6.)

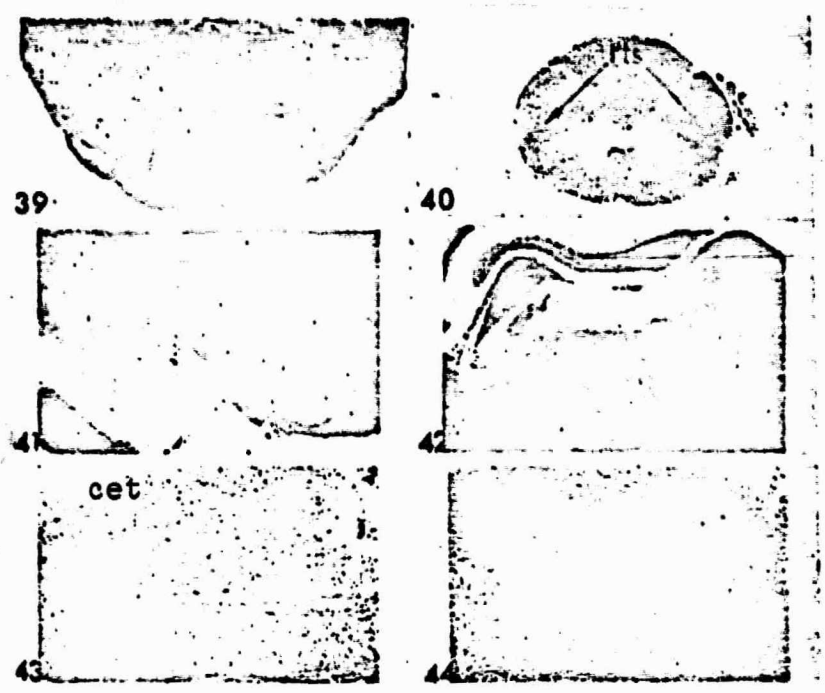

Figure 39-40. BP5. Transverse cuts to the superior bulb and the spinal column. Degeneration of the two rubrotegmentospinal bundles and the left rubro-olivary pathway (ro). Note a less significant degeneration in the left rubrotegmentospinal bundle (below the decussation) because of the damage to fibers on the tegmentary part of this bundle. (Color. Osmic acid. Gr. x 8, resp.)

Figure 41. BP70. Transverse cut to the mesencephalon. Ventromedian tegmentary lesion having spared the nigostriate fibers but extensively damaged the descending rubral efferent nerves and corresponding ascending cerebellofugal nerves. (Color. Klüver modif. Gr x 6.)

Figure 42-44. BP70. Transverse cuts to the upper pons illustrating the absence of left rubro-olivary fibers (ro) and of the right caudate efferent tegmentary bundle (cet) (below the decussation). (Color. Klüver modif. Gr. x 10, x 60, x 60, resp.)

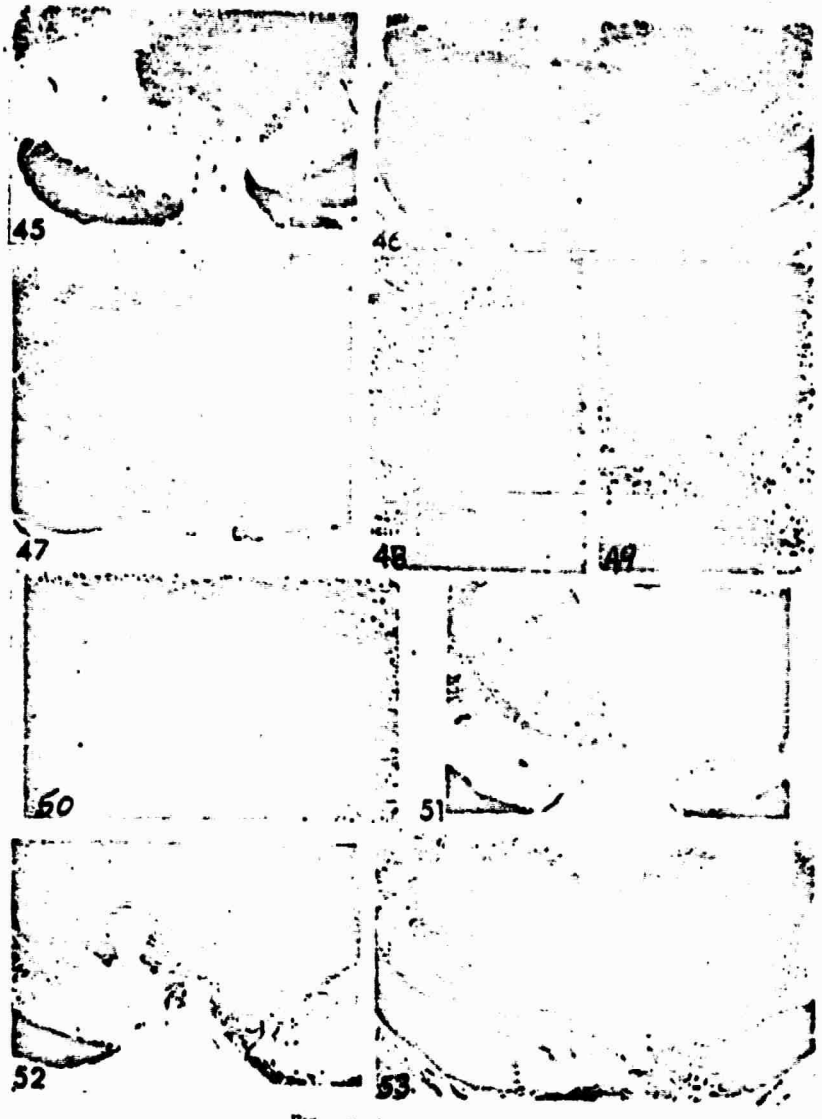

FIG. 45, 46, 47-50, 51, 52, 53.

[Captions for Figures are on following page]

Figure 45. BP65. Transverse cuts to the mesencephalon. Left ventrolateral tegmentary lesion having interrupted the left median lemniscus as well as the descending rubral efferent and ascending cerebellofugal nerves. (Color. Klüver modif. Gr. x 6.) /33

Figure 46. BP80. Transverse cut to the mesencephalon. Left lesion has crossed the median line and specifically involves the Wernekink decussation and the serotoninergic fibers on both sides. (Color. Klüver modif. Gr. x 6.)

Figure 47-50. BP80. Transverse cuts to the mesencephalon showing the intact neurons of the substantia nigra and the magnocellular red nucleus on both sides. Note the extreme paleness of the magnocellular red nuclei because of the interruption to the ascending cerebellofugal fibers. Figure 50 illustrates the left magnocellular red nucleus. (Color. Klüver modif. Gr. x 6, x 25, x 25, x 100, resp.)

Figure 51. BP80. Transverse cut passing through the parvocellular nuclei showing the paleness of these two nuclei as a result of damage to the Wernekink decussation. (Color. Klüver modif. Gr. x 6.)

Figure 52. BP36. Transverse cut to the mesencephalon. Left ventromedian tegmentary lesion having cut the corresponding nigrostriate pathway and the cerebellothalamic fibers on the rostral level of the corresponding parvocellular red nucleus. (Color. Klüver modif. Gr. x 6.)

Figure 53. BP79. Transverse cut to the mesencephalon illustrating a left ventromedian tegmentary lesion having cut the corresponding nigrostriate pathway. (Color. Klüver modif. Gr. x 8.)

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